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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,365	11/12/2001	Carol W. Readhead	18810-81606	9234

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/054,365	READHEAD ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *183-211* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *183-211* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Applicants' amendment to the claims and specification filed December 14, 2006 has been received and entered. Applicants have amended claims 183, 193-195, 203 and 204, while claims 1-182 have been canceled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2006 has been entered.

Election/Restrictions

Applicant's election of Group I was acknowledged. Claims 183-211 are pending and currently under examination as they are drawn to a non-human transgenic vertebrate.

Claims 183-211 are under examination.

Double Patenting

Claims 135-144, 152-161, 168-176 and 183-211 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 10/842,850 is withdrawn in view of abandonment of the co pending application '850.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 183-211 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by

weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 183-211 are broad in scope. The following paragraph will outline the full scope of the claims. These claims are broad in scope, encompassing any transgenic nonhuman vertebrate subsequently limiting to non-human primates, canines, felines, swine, pachyderms, equines, murine, ovines and bovine, or a bird selected from the group consisting of ducks, geese, turkeys and chickens. The breadth of independent claims are directed to transgenic nonhuman vertebrate, comprising a lentiviral vector comprising a polynucleotide encoding any gene product that is operably linked with any promoter. The claims are further directed to a progeny of nonhuman transgenic

vertebrate carrying in its germ cell a lentiviral vector comprising any polynucleotide sequence.

The specification asserts that this technology is applicable to the production of transgenic animals for use as animal models, and to the modification of the genome of an animal, by addition, modification, or subtraction of genetic material, often resulting in phenotypic changes (see para. 13 of the published application). The specification further asserts that generation of transgenic animals expressing agents that are of therapeutic benefit for use in human and veterinary medicine including the production of pharmaceuticals in domestic cows' milk, such as factors which enhance blood clotting for patients with types of haemophilia, or hormonal agents such as insulin and other peptide hormones (see para. 39 of the published application). While the specification has contemplated that methods of the invention may be used to create any nonhuman transgenic vertebrate of any species, the guidance provided by the specification correlated only to transfection of the testis of a male mouse to generate transgenic mouse comprising lentiviral-comprising GFP. It is unpredictable if genus of other nonhuman vertebrate could produce adequate amounts of exogenous protein that is to be harvested for pharmaceutical or industrial use or modification of the genome of an animal, by addition, deletion of genetic material, resulting in any specific phenotypic change. The specification provides guidance for a method of producing a transgenic mouse by injecting into testis of a male mouse a lentiviral vector comprising a xenogenic polynucleotide. The specification does not provide enabling disclosure for the claims of using resulting genus of transgenic nonhuman animal produced by the method

using lentiviral vector particularly since resulting phenotype of nonhuman vertebrate comprising any gene operably linked to any promoter would be unpredictable and artisan would have to perform undue experimentation to make use of the invention.

As a first issue, instant claim embrace any nonhuman transgenic vertebrate comprising a lentiviral vector comprising at last one xenogenic polynucleotide encoding any gene product. It is noted that claim 183-184, 187-, 189, 190-194, 197, 199-203, 206-211 are drawn to nonhuman transgenic vertebrate generated by administering into the testis lentiviral vector comprising at least one polynucleotide. The specification has exemplified administering genetic material (GFP) into the testis of a mouse and reverse transcriptase PCR (RTPCR) analysis of tissues obtained from the testis showed presence of GFP in the injected testes, but not in the control testes. It is noted that specification only teaches administration of lentiviral vector directly into testis resulting in expression of gene in the testis. It is emphasized that neither prior art nor instant specification teaches that such a F0 founder animal would show presence of polynucleotide in most of the other cells as required by the preamble of the claims. In other words, these would be founder animal and not transgenic nonhuman vertebrate as required by the claim.

As a second issue, instant claims are drawn to any transgenic nonhuman vertebrate comprising lentiviral vector comprising polynucleotide encoding a gene or desired product of any phenotype. . Subsequent claims limit the nonhuman vertebrate to include mammal selected from the group consisting of non-human primates, canines, felines, swine, pachyderms, equines, murine, ovines and bovine, ducks, geese, turkeys

and chickens. It is noted that specification contemplated DNA sequences capable of imparting novel genetic modification, or biologically functional characteristic to the recipient animal. The novel genetic modification or characteristic may be encoded by one or more genes, or may be caused by removal or mutation of one or more genes. The specification also contemplated a gene's function may be expressed to inactivate one of a pair of genes (alleles), or inactivation of genetic material by mutation or deletion of gene sequences, or by expression of a dominant negative gene product or artificially induced mutations or variations (see para. 29-29 of the specification). The specification also contemplates expression of a previously unexpressed trait, augmentation or reduction of an expressed trait, over expression or under expression of a trait, ectopic expression (see para. 31 of the specification). The specification has exemplified a method to make transgenic mouse comprising GFP. However, prior and post filing art recognized only mouse as a routinely manipulated animal and recognized the unpredictability of making transgenic animals with a specific phenotype. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). Mullins et al states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without

general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall. Theriogenology 45:61, par 2, line 9 to p. 62, line 3, 1996.) Mullins et al disclose that "the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to the another" (Mullins et al. J Clin Invest 98:S39 summary, 1996). This observation is specifically supported by Hammer et al. (Journal of animal Science, 986, 63, 269-278) who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al (Mol Endocrinol. 1988; 2(3): 277-83) report a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (p. 277, summarized in abstract). The observation is further supported by Mullins et al (Journal of Clinical Investigation, 1996, 97, 1557-1560), who report on transgenesis in the rat and larger mammals. Mullins et al. state "a given construct may react very differently from one species to another" (see Summary section). It is also noted that the specification contemplated deleting or mutating a gene by delivering the vector of the invention comprising a polynucleotide. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential

in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, at the time of filing, the resulting phenotype of a knockout nonhuman vertebrate was considered unpredictable and it was confounded by multiple compensatory pathways. The specification does not teach any transgenic nonhuman vertebrate comprising any disruption that would result in expected phenotype. An Artisan of skill would need to perform further research upon the nonhuman vertebrate obtained by the process disclosed in the instant application in order to determine the correlation between the transgene and the observed phenotypes or effect. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make use of the invention. An artisan would have to perform undue experimentation to determine the appropriate elements that would specifically express genus of different genes in any nonhuman vertebrate animal showing expected phenotype. Absent of evidence to the contrary, it is not clear that resulting phenotype of a nonhuman vertebrate comprising genus of gene with known or unknown biological function in presence of any promoter would result in any specific phenotype particularly in view of unpredictably expressed in transgenic art. An artisan would not know how to

use resulting transgenic nonhuman vertebrate and therefore would have to perform undue experimentation to determine how to use the resulting transgenic nonhuman vertebrate obtained from the method disclosed in the instant invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 183-2111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 183, 185, 193-196 and 203-205 are vague and indefinite to the extent it is unclear whether vector sequence or sequence encoding gene product is xenogenic. The meets and bounds of term xenogenic with respect to vector comprising at least one xenogenic polynucleotide are unclear, particularly since virus sequence as well as sequence encoding gene product both could be xenogenic to the host. It is further unclear whether sequence encoding gene product is xenogenic to the viral sequence or host. Claim 184-186-192, 197-202 and 206-211 are directly or indirectly dependent on independent claims. Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 183-211 are rejected under 35 U.S.C. 102(e) as being anticipated by Brinster et al. (US Patent 5,858,354, art of record) and Deboer et al. (US Patent

5,741,957, art of record) is withdrawn in view of amendment to the claim now requiring presence of lentiviral vector in the genome of the nonhuman vertebrate.

Claims 184-211 rejected under 35 U.S.C. 102(b) as being anticipated by Leder et al. (US Patent 4,736,866) is withdrawn in view of amendments to the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 183-211 are rejected under 35 U.S.C. 102(b) as being anticipated by Jolicoeur et al (Us Patent 5574206 dated 11/12/1996).

Jolicoeur et al teach a non-human transgenic mammal in which the germ cells and somatic cells carry a transgene capable of expressing non-infectious HIV ribonucleic acid (having the entire encoding sequence of the HIV genome), and the complementary proteins, in the cells. The transgene is introduced into the animal, or an ancestor of the animal (see col. 4, lines 4-11). In addition, Jolicoeur et al also contemplate using transgene comprising surrogate promoter/tissue-specific enhancer to drive expression of the HIV genome is the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequence. This promoter is known to be tissue specific toward various epithelial and hemopoietic tissues, some of which naturally support lentivirus (and especially HIV)

replication (see col. 8, line 60-65). It is noted that Jolicoeur et al disclose a mouse in which the germ cells and somatic cells carry at least one copy of a single transgene that comprising (i) a HIV DNA genome from which is deleted the 5'-LTR, a portion of the 5' leader sequence, and a portion of the 3'-LTR, whereby said HIV DNA and its RNA transcript are rendered non-infectious, (ii) the MMTV LTR promoter operatively linked to the 1' end of said DNA, and (iii) the SV40 poly(A) addition signal operatively linked to the 3' end of said DNA (see claims 1 and 2). In the instant case, claims are directed to a nonhuman vertebrate comprising lentiviral vector comprising xenogenic polynucleotide. It is unclear whether polynucleotide is xenogenic to the vector or host nonhuman vertebrate. Therefore, xenogenic could broadly be interpreted to embrace a sequence from another species. In the instant case, a reasonable interpretation would be a nonhuman vertebrate infected with any species of virus and its sequence in germ cell, particularly since claims merely require presence of virus in the germ cell. Thus, mouse or nonhuman vertebrate disclosed by Jolicoeur et al meet the structural limitation of instant claims. It is emphasized that the progeny of the transgenic mouse disclosed by Jolicoeur et al would also contain the virus in the germ cell as well as somatic cell. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re*

Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Jolicoeur et al anticipate claims 183-211.

Claims 183-184, 187, 189, 190-194, 197, 199-203, 206-211 are rejected under 35 U.S.C. 102(b) as being anticipated by Jordan et al (Journal of Virology, 1995, 69 (11), 7328–7333).

Jordan et al. disclose a cat that is infected with feline immunodeficiency virus (FIV). It is noted that Jordan et al teach the presence of virus in seminal plasma and seminal cells (see abstract and Table 1 and 2). Jordan et al also detected FIV in semen of cats at 12 and 24 months post infection (see page 7331, col. 2, last para.). Therefore, practicing the methods disclosed by Jordan result in a nonhuman vertebrate comprising germ cells that has been infected with FIV. In the instant case, claims are directed to a nonhuman vertebrate comprising lentiviral vector comprising xenogenic polynucleotide. It is unclear whether polynucleotide is xenogenic to the vector or host nonhuman vertebrate. Therefore, xenogenic could broadly be interpreted to embrace a sequence from another species. In the instant case, a reasonable interpretation would be a nonhuman vertebrate infected with any species of virus and its sequence in germ cell, particularly since claims merely require presence of virus in the germ cell. It is noted that these claims do not require viral vector to be present in the somatic cells. Thus, cat disclosed

by Jordan et al meet the structural limitation of instant claims. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Jordan et al anticipate claims 183-184, 187, 189, 190-194, 197, 199-203, 206-211.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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